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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P 687 PC00	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/DK 03/00448	International filing date *(day/month/year)* 27.06.2003	Priority date *(day/month/year)* 27.06.2002
International Patent Classification (IPC) or both national classification and IPC C12Q1/68		
Applicant AARHUS UNIVERSITET et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 10 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 8 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
14.01.2004	14.12.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Schmitt, C Telephone No. +49 89 2399-7351

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/DK 03/00448

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-61 as originally filed

Claims, Numbers

1-31 received on 20.09.2004 with letter of 20.09.2004

Drawings, Sheets

1/4-4/4 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☒ furnished subsequently to this Authority in written form.

   ☒ furnished subsequently to this Authority in computer readable form.

   ☒ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☒ the claims, Nos.: 32-37

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 1-21 (all partially), 22-25 (all completely)

   because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☒ the claims, or said claims Nos. 1-21 (all partially), 22-25 (all completely) are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 1-21 (all partially)

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-21 (all partially), 26-31
	No:	Claims	-
Inventive step (IS)	Yes:	Claims	1-21 (all partially)
	No:	Claims	26-31
Industrial applicability (IA)	Yes:	Claims	1-31
	No:	Claims	-

2. Citations and explanations

   see separate sheet

Re Item I

Basis of the report

The basis for this report is amended claims 1-31 filed with the letter dated 20.09.2004.

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

III.1. In view of the International Search Report, claims 1-21 were only searched with respect to the polymorphisms RAli1, RAle6, **AES-1e3**, ASE-1e1 and the XPD-4bp deletion (i.e. examples 1-3 and 10).
The term "**AES-1e3**" is not found in the present application. The present Examination Authority considers therefore that the term "**AES-1e3**" used in Sheet 210 of the ISR is a spelling mistake and should be read "**ASE-1e3**". Furthermore, from the description it appears that the polymorphism **ASE-1e3a** (Table 1c) is localized at position 36926 of SEQ ID NO:1 whereas the polymorphism **ASE-1e3b** is not localized in any of SEQ ID NO: 1 or 2.
In the following, the present Examining Authority, therefore, assumed that the polymorphism **ASE-1e3** which was searched is the polymorphism **ASE-1e3a** localized at position 36926 of SEQ ID NO:1, said sequence of SEQ ID NO:1 being comprised in the sequence of SEQ ID NO:2.

Claims, or parts of claims, relating to subject-matter in respect of which no international search report has been established need not to be the subject of an international preliminary examination (Rule 66.1(e) PCT).
Thus, an opinion on claims 1-21 is only formulated with respect to the subject-matter that was searched, namely with respect to the polymorphisms denoted RAli1, RAle6, ASE-1e3a, ASE-1e1 and the XPD-4bp deletion, wherein the polymorphism RAli1 is located at position 15798 in SEQ ID NO 1, the polymorphism RAle6 is located at position 7887 in SEQ ID NO 1, the polymorphism ASE-1e3a is located at position 36926 in SEQ ID NO 1, the polymorphism ASE-1e1 is located at positions 34858 and 36241 in SEQ ID NO 1 and the polymorphism XPD-4bp is located at position 323-326 in SEQ ID NO 2.

III.2. The present application only shows that specific genotypes, i.e. homozygote for $RAli1^A$; homozygote for $RAli1^A$ and $RAle6^A$, and homozygote for the complete 167 bp fragment (i.e.

XPD-4bp deletion/insertion polymorphism) are associated with basocellular carcinoma (i.e. skin cancer of epithelial origin) or breast cancer (examples 1-3 and 10). These polymorphims are encompassed by the sequence of SEQ ID NO: 2. No data are given for any of the following polymorphisms denoted RAIi1, RAIe6, ASE-1e3a, ASE-1e1 and the XPD-4bp as being linked to lung cancer or colon cancer. Furthermore, the application fails to provide any data showing that the polymorphisms ASE-1e3a or ASE-1e1 are linked to basocellular carcinoma or breast cancer.

The description gives guidance to the skilled person how to identify polymorphisms linked to an increase risk of developing cancer on the basis of statistical analysis of the incidence of a particular allele in two groups of individuals with and without cancer, respectively.

However, even if guidance are given in the description how to assess if a certain polymorphism is linked with a risk of developing cancer, the skilled person will have to assess every single polymorphism for its possible association with a certain phenotype.

It is not because two or more particular alleles at two or more neighbouring loci show allelic association (i.e. linkage disequilibrium) that an additional allele of an additional locus which is in close vicinity will also be in linkage disequilibrium. Even if the probability exists, that a further polymorphism, which is in close vicinity with one that has been shown to be associated with a disease, will also be associated with such a disease, the probability that such further polymorphism is not associated with the disease also exists. Thus, the skilled person will have to assess every single polymorphism for its possible association with a certain phenotype.

Even if the present application shows that certain polymorphisms are associated with certain cancers, the skilled person would not be able without undue burden to identify or assess additional polymorphisms for their association with skin cancer, breast cancer, colon cancer and lung cancer.

Claims 1-21 cover subject-matter not sufficiently disclosed in the sense of Article 5 PCT, and therefore are, in addition, not supported by the description within the meaning of Article 6 PCT.

An opinion on novelty and inventive step of claims 1-21 will therefore only be given with respect to the subject-matter that was searched, and appears to be clear and supported.

III.3. Furthermore, the present application only shows that particular polymorphisms or genotypes are linked to an increased risk to skin cancer of epithelial origin or breast cancer (see item **III.2**, above). However, the present application fails to provide any data as to any polymorphism which is linked to the prognosis of a disease, in particular said cancers, or to

the treatment response of an individual suffering from a cancer.
Claims 22-25 are therefore not supported under Article 6 PCT and the application does not meet the requirements of Article 5 PCT.
No opinion on novelty and inventive step will therefore be given for claims 22-25.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: YIN JIAOYANG ET AL: 'Multiple single nucleotide polymorphisms on human chromosome 19q13.2-3 associate with risk of basal cell carcinoma.'
CANCER EPIDEMIOLOGY BIOMARKERS AND PREVENTION, vol. 11, no. 11, November 2002, pages 1449-1453.

D2: NEXO BJORN A ET AL: 'A specific haplotype of single nucleotide polymorphisms on chromosome 19q13.2-3 encompassing the gene RAI is indicative of post-menopausal breast cancer before age 55.'
CARCINOGENESIS, vol. 24, no. 5, May 2003, pages 899-904.

D3: ROCKENBAUER ESZTER ET AL: 'Association of chromosome 19q13.2-3 haplotypes with basal cell carcinoma: Tentative delineation of an involved region using data for single nucleotide polymorphisms in two cohorts.' CARCINOGENESIS, vol. 23, no. 7, July 2002, pages 1149-1153.

D4: YIN JIAOYANG ET AL: 'Twelve single nucleotide polymorphisms on chromosome 19q13.2-13.3: Linkage disequilibria and associations with basal cell carcinoma in Danish psoriatic patients.'
BIOCHEMICAL GENETICS, vol. 41, no. 1-2, February 2003, pages 27-37.

D5: BERGAMASCHI DANIELE ET AL: 'iASPP oncoprotein is a key inhibitor of p53 conserved from worm to human.'
NATURE GENETICS, vol. 33, no. 2, February 2003, pages 162-167.

D6: SHEN M RICHARD ET AL: 'Nonconservative amino acid substitution variants exist at polymorphic frequency in DNA repair genes in healthy humans'
CANCER RESEARCH, vol. 58, no. 4, 15 February 1998, pages 604-608.

D7: VOGEL ULLA ET AL: 'Polymorphisms of the DNA repair gene XPD: Correlations with risk of basal cell carcinoma revisited'
CARCINOGENESIS (OXFORD), vol. 22, no. 6, June 2001, pages 899-904.

D8: DYBDAHL MARIANNE ET AL: 'Polymorphisms in the DNA repair gene XPD: Correlations with risk and age at onset of basal cell carcinoma'
CANCER EPIDEMIOLOGY BIOMARKERS AND PREVENTION, vol. 8, no. 1, January 1999, pages 77-81.

D9: WO 95 16791 A (UNIV MCGILL ;POIRIER JUDES (CA)) 22 June 1995.

D10: CHEN PENGCHIN ET AL: 'Association of an ERCC1 polymorphism with adult-onset glioma'
CANCER EPIDEMIOLOGY BIOMARKERS AND PREVENTION, vol. 9, no. 8, August 2000, pages 843-847.

D11: YANG JIAN-PING ET AL: 'Identification of a novel inhibitor of nuclear factor-kappaB, RelA-associated inhibitor'
JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 274, no. 22, 28 May 1999, pages 15662-15670.

D12: EP-A-1 146 054 (ONO PHARMACEUTICAL CO) 17 October 2001.

D13: BREWSTER A M ET AL: 'The association between polymorphisms in the xeroderma pigmentosum group D gene and risk of breast cancer'
AMERICAN JOURNAL OF EPIDEMIOLOGY, vol. 153, no. 11 Supplement, 1 June 2001 (2001-06-01), page S198 XP002261357 Joint Meeting of the Society for Epidemiologic Research, American College of Epidemiology, Epidemiol; Toronto, Canada; June 13-16, 2001 ISSN: 0002-9262

D14: BUTKIEWICZ DOROTA ET AL: 'Genetic polymorphisms in DNA repair genes and risk

of lung cancer'
CARCINOGENESIS, vol. 22, no. 4, April 2001, pages 593-597.

V.1. Novelty and inventive step of product claims 26-31.

Claims 26-31 are considered new in the sense of Article 33(2) PCT as their features are not disclosed in any available prior art documents.

Independent claim 26 relates to primer or probe selected from SEQ ID NOs: 7-21, wherein, SEQ ID Nos: 7-10 are primers/probes suitable for the detection of RAIi1 polymorphism, SEQ ID Nos: 11-14 are primers/probes suitable for the detection of ASE1e1 polymorphism, SEQ ID Nos: 15-17 are primers/probes suitable for the detection of RAIe6 polymorphism and SEQ ID Nos: 18-21 are primers/probes suitable for the detection of RAI-5'2 and RAI-5'3 polymorphisms.
As the presently identified polymorphisms denoted ASE1e1, RAI-5'2 and RAI-5'3 lack any feature which could go beyond the well known features common to all polymorphisms, i.e. their possible use as genetic markers, the claimed sequences of SEQ ID Nos: 11-14 and 18-21 do not appear to be associated with any feature which could go beyond the well known features of their possible use to detect polymorphisms, the only underlying technical problem that can be recognised is the provision of further primer or probe suitable for the detection of polymorphisms. To establish inventive activity, the provision of a sequence must be justified by the technical purpose, i.e. by a hitherto unknown or unexpected technical effect, caused by technical features which distinguish the claimed molecules from numerous other ones. Due to the absence of any unexpected defined technical effect (i.e. detection of a specific polymorphisms which are linked to cancer), the provision of the present sequences of SEQ ID Nos: 11-14 and 18-21 amounts to nothing more than an arbitrary selection.

Independent claim 26 is therefore considered to lack an inventive step in the sense of Article 33(3) PCT.

The additional features set out in dependent claims 27-30 are common practice in the art. Claims 27-30 appear also not inventive in the sense of Article 33(3) PCT.

Lastly, the incorporation of not inventive primers or probes into a kit would be obvious to the skilled person. Claim 31 is therefore not inventive in the sense of Article 33(3) PCT.

The applicant attention is drawn to the fact that primers or probes of SEQ ID Nos:7-10, 15-17 appear to be inventive in the sense of Article 33(3) PCT as they have an unexpected effect over the prior art, i.e. they allow the detection of polymorphisms RAli1 and RAle6 which are linked to basocellular carcinoma (i.e. skin cancer of epithelial origin) or breast cancer.

V.2. Novelty and inventive step of claims 1-21.

Documents D6-D8, D13 and D14 disclose various polymorphisms in the XPD gene which are linked to basocellular carcinoma, breast or lung cancers (see abstracts of said documents). However, none of these document discloses the existence of the XPD-4bp polymorphism linked to cancer or suggest that this polymorphism could exist.
Claims 1-21 are thus considered new in the sense of Article 33(2) PCT.

In view of documents D6-D8, D13 and D14, the problem to be solved by claim 1 may be seen as the provision of an alternative method for estimating the basocellular carcinoma or breast cancer risk in an individual.
This problem seems to be solved in view of the overall teaching of the application. None of the available document discloses the features that in combination with D6-D8, D13 or D14 would lead the skilled person to assess specifically the polymorphism sequence RAli1, RAle6 or XPD-4bp.

Hence, claim 1-21 limited to a method for estimating the skin cancer of epithelial origin or breast cancer risk of individual, comprising assessing the presence of the specific genotypes which appear to be linked to said risk, i.e. homozygote for $RAli1^A$ or for $RAli1^A$ and $RAle6^A$, and homozygote for the complete 167 bp fragment (i.e. XPD-4bp deletion/insertion polymorphism)(see also item III.2) would appear to involve an inventive step (Article 33(3) PCT).

V.3. Further comments

Trivial names for polymorphisms, such as RAli1, RAle6, ASE-1e3, ASE-1e1 and XPD-4bp are deemed to be unclear in the sense of Article 6 PCT. Said polymorphisms should be clearly defined by their position within SEQ ID NO: 1 or SEQ ID NO:2.

The validity of the priority claimed by the present application has not been checked.

Should the claimed priority be invalid, then documents D1-D5, cited as P,X documents in the International Search Report, would appear to be highly relevant for the question of novelty and/or inventive step of present claims 1-31.

Agent's file reference: P[redacted]C00
International application No. PCT/DK03/00448
Applicant: Aarhus Universitet et al.

10/519505
DT01 Rec'd PCT/PTO 27 DEC 2004

Amended Claims

1. A method for estimating the skin cancer, lung cancer, breast cancer and colon cancer risk of an individual comprising

- assessing in the genetic material of a sample from said individual a sequence polymorphism

  - in a region corresponding to SEQ ID NO: 2, or a part thereof, or
  - in a region complementary to SEQ ID NO: 2, or a part thereof, or
  - in a transcription product from a sequence in a region corresponding to SEQ ID NO: 2, or a part thereof, or,
  - or translation product from a sequence in a region corresponding to SEQ ID NO: 2, or a part thereof,
  - obtaining a sequence polymorphism response,

- estimating the skin cancer, lung cancer, breast cancer and colon cancer risk of said individual based on the sequence polymorphism response.

2. The method according to claim 1, wherein a sequence polymorphism is assessed

- in a region corresponding to SEQ ID NO: 1, or a part thereof, or
- in a region complementary to SEQ ID NO: 1, or a part thereof, or
- in a transcription product from a sequence in a region corresponding to SEQ ID NO: 1, or a part thereof, or
- or translation product from a sequence in a region corresponding to SEQ ID NO: 1, or a part thereof.

3. The method according to claim 1, wherein the cell sample is a blood sample, a tissue sample, a sample of secretion, semen, ovum, a washing of a body surface, such as a buccal swap, a clipping of a body surface, including hairs and nails.

4. The method according to any of the preceding claims, wherein the cell is selected from white blood cells and tumor tissue.

5. The method according to any of the preceding claims, wherein the sequence polymorphism comprises at least one mutation base change.

6. The method according to any of the preceding claims, wherein the sequence polymorphism comprises at least two base changes.

7. The method according to any of the preceding claims, wherein the sequence polymorphism comprises at least one single nucleotide polymorphism.

8. The method according to any of the preceding claims, wherein the sequence polymorphism comprises at least two single nucleotide polymorphisms.

9. The method according to any of the preceding claims, wherein the sequence polymorphism comprises at least one tandem repeat polymorphism.

10. The method according to any of the preceding claims, wherein the sequence polymorphism comprises at least two tandem repeat polymorphisms.

11. The method according to any of the preceding claims, wherein the assessment is conducted by means of at least one nucleic acid primer or probe, such as a primer or probe of DNA, RNA or a nucleic acid analogue such as peptide nucleic acid (PNA) or locked nucleic acid (LNA).

12. The method according to claim 11, wherein the nucleotide primer or probe is capable of hybridising to a subsequence of the region corresponding to SEQ ID NO: 1, or a part thereof, or a region complementary to SEQ ID NO:1.

13. The method according to claim 11, wherein the primer or probe has a length of at least 9 nucleotide or peptide monomers.

14. The method according to any of the preceding claims 11-13, wherein at least one primer or probe is capable of hybridising to a subsequence selected from the group of subsequences

1. GCTCTGAAAC TTACTAGCCC(A/G)GTATTTATGG AGAGGCATTT
2. GTGGTCAAAT TCTCATTCAT CGTGG (T/C) CCAGGCAAGC ACACTTCCTC
3. ACCCTGAGGT GAGCACCTGT TCCTT(C/T) TCCTTGCCCT TAGCCCA-GAG GTAGA
4. GGGCAGGGGT TTGTGCCTCC AATGA (G/A) CACAAGCTCC CCCTGCCCCC CAACT
5. CCTGGCGGTG GCCGTCACCA GCTTT (T/C) GGGGGTGTTT GGGAAGCTGG
6. CTCCAGCCCC ACTGTTCCCT (A/G) GGCCCTATTG GTCCCCCTGG
7. ACAAGGAGGA GGCAGAAGTG AGGTT (G/C) AAACCCACTG CCCAATC-TTA
8. CCAACACGGT GAAACCCCGT CTGTA(T/C)TAAAAATACA AAAATTAGCC
9. AATCCAGGAC CCCATAATCT TCCGT (C/T) ATCTAAAACA ATA-ATGGTGA
10. CCCAAGGGGG CGAGGGGAGG GTGAA (A/G)GGGTGGGACG GGGGCAGCCG
11. GAAGTGAGAA GGGGGCTGGG GGTCG (G/-) CGCTCGCTAG CGGGCGCGGG
12. CGCACGCGCA GTATCCCGAT TGGCT (C/G)TGCCCTAGCG GATT-GACGGG
13. AACTCCTGGG TTCGATCAAT ACTCA (GACA/-) ATCTTGGCAG GCGCAGGAGG
14. GCTGGGATTA CAGGCTTGAG CCACC (A/G) CGCCCGGCCT GCAAAGCCAT
15. TTTTGTATCT TTAGTAGAGA CAGG (T/G) TTTCTCCATG TTGGTCAGGC
16. GCCTCAGCCT CCCGAGTAGC TGAGACT (C/A) CAGGTGCCCG CCAC-CACGCC
17. TGAAATTGTA GGTTGAGAGG CCAGGCG (C/T) GGTGCTCACG CCTGTAATTT
18. GTTTATAAAC ATTAAACCAG (T/A) GCTGTGTGAA GGCACTTAAT

19. CCGTCTCTAT TAAAAATATA AAA (A/C) AATTTAGCCG GGTGTAGCGG
20. GGGAGGCTCG AGGCGGGC (A/G) GATTGCATGA GCTCAGGATT
21. TCCCAAGTTT CAGGGCCCAA (T/G) ATTCTCAAAT CACAGGATTC
22. TGCAGTGAGC TGAGATCGC (A/G) CCACTGCACT CCAGCCTGGG
23. TCTTAGGACG CATGGGGGT (T/G) GAGAGAACGG GGAGATAGAC
24. CTGGGTTCTA GAACTACC (C/T) ATGCAAACCC AGCTGTTTCC
25. ATTCTGCCCT GGGTTCTAGA ACTACCT (C/A) TGCAAACCCA GCTGTTTCCC
26. GCTGTTTCCC ACCCCATAAG GCA (A/G) TAGGGGAGCC CACCTCCGCC
27. GACCTAGAAG ATCGGTCGAG A (C/T) AGCAGCTTGA GGCTGGCAGG
28. CTGGCCAGGA ATGCAGTCGG GTCAC (C/T) CTGTCTAGCC ACCGTCTCGC
29. GGGAGGAGTC GCCGATCAGG (C/T) CCCTTCCTGA AAGTCATCGA
30. GCAGCCCGGG CTACAGGGTT (A/G) CCTGAGGTGT GGGTCCCAGG
31. TAGAAATACT AACAAAGGGC (T/C) GTGGGTTTCT CCCCCTGCTT
32. ACAGGAGAGG GAAGGTTTTTTG (A/T) TTTTTTTTTT GTTTTTTTTT
33. GAAGAGGAAG AAGCCCAAAG GGA (A/C) AGAAACCTTC GAGCCA-GAAG
34. GCGCCTCAAC AGCCAGAAGG AGCG (A/G) AGCCTCAGGC CCAGG-CAGCT
35. TTGAGACTCT CTGTTTGAT (A/G) CTTCACTCAG AAGGTGCTTC
36. AGGCCAGGCT CCTGCTGGCT G (C/G) GCTGGTGCAG TCTCTGGGGA
37. CCCCTATACC CTCAAGCAT (C/T) TATCCATTGA GTTACAAACA
38. ACCATCCCCC GCCTTCCGTT (A/C) GTCCGGCCCC CGAGGCTAGC

or to a sequence complementary to any of the subsequences.

15. The method according to claim 14, wherein at least one nucleotide probe is selected from the group consisting of

1. TGAAATTGTA GGTTGAGAGG CCAGGCG (C/T) GGTGCTCACG CCTGTAATTT
2. GTTTATAAAC ATTAAACCAG (T/A) GCTGTGTGAA GGCACTTAAT
3. CCGTCTCTAT TAAAAATATA AAA (A/C) AATTTAGCCG GGTGTAGCGG

4. GGGAGGCTCG AGGCGGGC (A/G) GATTGCATGA GCTCAGGATT
5. TCCCAAGTTT CAGGGCCCAA (T/G) ATTCTCAAAT CACAGGATTC
6. TGCAGTGAGC TGAGATCGC (A/G) CCACTGCACT CCAGCCTGGG
7. TCTTAGGACG CATGGGGGT (T/G) GAGAGAACGG GGAGATAGAC
8. CTGGGTTCTA GAACTACC (C/T) ATGCAAACCC AGCTGTTTCC
9. ATTCTGCCCT GGGTTCTAGA ACTACCT (C/A) TGCAAACCCA GCTGTTTCCC
10. GCTGTTTCCC ACCCCATAAG GCA (A/G) TAGGGGAGCC CACCTCCGCC
11. GACCTAGAAG ATCGGTCGAG A (C/T) AGCAGCTTGA GGCTGGCAGG
12. CTGGCCAGGA ATGCAGTCGG GTCAC (C/T) CTGTCTAGCC ACCGTCTCGC
13. GGGAGGAGTC GCCGATCAGG (C/T) CCCTTCCTGA AAGTCATCGA
14. GCAGCCCGGG CTACAGGGTT (A/G) CCTGAGGTGT GGGTCCCAGG
15. TAGAAATACT AACAAAGGGC (T/C) GTGGGTTTCT CCCCCTGCTT
16. ACAGGAGAGG GAAGGTTTTTTG (A/T) TTTTTTTTTT GTTTTTTTTT
17. GAAGAGGAAG AAGCCCAAAG GGA (A/C) AGAAACCTTC GAGCCA-GAAG
18. GCGCCTCAAC AGCCAGAAGG AGCG (A/G) AGCCTCAGGC CCAGG-CAGCT

or to a sequence complementary to any of the subsequences.

16. The method according to claim 15, wherein at least one nucleotide probe is selected from the group consisting of

1. GTTTATAAAC ATTAAACCAG (T/A) GCTGTGTGAA GGCACTTAAT
2. CCGTCTCTAT TAAAAATATA AAA (A/C) AATTTAGCCG GGTGTAGCGG
3. GGGAGGCTCG AGGCGGGC (A/G) GATTGCATGA GCTCAGGATT
4. TCCCAAGTTT CAGGGCCCAA (T/G) ATTCTCAAAT CACAGGATTC
5. TGCAGTGAGC TGAGATCGC (A/G) CCACTGCACT CCAGCCTGGG

or to a sequence complementary to any of the subsequences.

17. The method according to any of the preceding claims, wherein at least one sequence polymorphism is assessed in a region corresponding to SEQ ID NO: 1 position 1521-37752 (r).

18. The method according to any of the preceding claims, wherein at least one sequence polymorphism is assessed in a region corresponding to SEQ ID NO: 1 position 7760-22885 (RAI).

19. The method according to any of the preceding claims, wherein at least one sequence polymorphism is assessed in a region corresponding to SEQ ID NO: 1 position 34391- 37752.

20. The method according to any of the preceding claims, wherein at least two different probes are used, one probe being selected from the probes as defined in any of claims 13-16, and the other probe being capable of hybridising to a sequence different from SEQ ID NO: 1, or a part thereof, or to a sequence complementary to a region different from SEQ ID NO: 1, or a part thereof,.

21. The method according to claim 1, wherein the translational product from a sequence in a region corresponding to SEQ ID NO: 1, or a part thereof, is an antibody, such as a monoclonal or polyclonal antibody.

22. A method for estimating the disease prognosis of an individual comprising

- assessing in the genetic material of a sample from said individual a sequence polymorphism
  - in a region corresponding to SEQ ID NO: 2, or a part thereof, or
  - in a region complementary to SEQ ID NO: 2, or a part thereof, or
  - in a transcription product from a sequence in a region corresponding to SEQ ID NO: 2, or a part thereof, or
  - or translation product from a sequence in a region corresponding to SEQ ID NO: 2, or a part thereof,
- obtaining a sequence polymorphism response,

- estimating the disease prognosis of said individual based on the sequence polymorphism response.

23. The method according to claim 22, wherein the method has any of the features as defined in any of the claims 2-21.

24. A method for estimating a treatment response of an individual suffering from cancer to a disease treatment, comprising

- assessing in the genetic material of a sample from said individual a sequence polymorphism

  - in a region corresponding to SEQ ID NO: 1, or a part thereof, or
  - in a region complementary to SEQ ID NO: 1, or a part thereof, or
  - in a transcription product from a sequence in a region corresponding to SEQ ID NO: 1, or a part thereof, or
  - or translation product from a sequence in a region corresponding to SEQ ID NO: 1, or a part thereof,

- obtaining a sequence polymorphism response,

- estimating the individual's response to the disease treatment based on the sequence polymorphism response.

25. The method according to claim 24, wherein the method has any of the features as defined in any of the claims 2-21.

26. A primer or probe for detecting polymorphisms for use in a method as defined in any of the claims above, said primer or probe being selected from

TGGCTAACACGGTGAAACC(SEQ ID NO:7)
GGAATCCAAAGATTCTATGATGG(SEQ ID NO:8)
GGGAGGCGGAGCTTGCAGTGA (SEQ ID NO:9)
CTGAGATCGCACCACTGCAC (SEQ ID NO:10)
GGTTTTCTGCTCTGCACACG (SEQ ID NO:11)

CCTTTCTCCTTCCACCAACG (SEQ ID NO:12)

CGGGCTACAGGGTTACCTGAG (SEQ ID NO:13)

TCTGCAACCTGGTGCGAGCAGC (SEQ ID NO:14)

CCTACCACCATCATCACATCC (SEQ ID NO:15)

GCCTTGCCAAAAATCATAACC (SEQ ID NO:16)

CCTCTCCCCAATTAAGTGCCTTCACACAGC (SEQ ID NO:17)

AGCCAGGGAGGTTGAGGCT (SEQ ID NO:18)

AGACAGCCCTGAATCAGCAC (SEQ ID NO:19)

GCAATGAGCCGAGATAGAA (SEQ ID NO:20)

TGGCTAGCCCATTACTCTA (SEQ ID NO:21)

27. The primer or probe according to claim 26, wherein the probe is operably linked to at least one label, such as operably linked to two different labels.

28. The probe according to claim 27, wherein the label is selected from TEX, TET, TAM, ROX, R6G, ORG, HEX, FLU, FAM, DABSYL, Cy7, Cy5, Cy3, BOFL, BOF, BO-X, BO-TRX, BO-TMR, JOE, 6JOE, VIC, 6FAM, LCRed640, LCRed705, TAMRA, Biotin, Digoxigenin, DuO-family, Daq-family.

29. The primer or probe according to any of claims 26-28, wherein the primer or probe is operably linked to a surface.

30. The primer or probe according to claim 29, wherein the surface is the surface of microbeads or a DNA chip.

31. A kit for use in a method as defined in any of the claims above, comprising at least one primer or probe, said probe being as defined in any of claims 26-30, and optionally further amplifying means for nucleic acid amplification.